Minimizing Inappropriate or “Unnecessary” Implantable Cardioverter-Defibrillator Shocks

Appropriate Programming

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Life-saving shocks are the *raisons d’être* of implantable cardioverter-defibrillators (ICDs). Paradoxically, shocks also cause much of the morbidity associated with ICDs. Consistently, shocks reduce quality of life, and rarely, they may cause proarrhythmia. Additionally, shocks have been reported to be associated with excess mortality. Experts disagree about whether shocks are responsible for this excess mortality, but they do agree that ICDs should deliver the fewest shocks necessary to protect patients from ventricular tachycardia (VT) or ventricular fibrillation (VF).

Minimizing ICD shocks requires a comprehensive approach, beginning with patient selection, general medical care (eg, preventing electrolyte abnormalities), and general cardiac care (preventing ischemia and treating heart failure). It includes the use of antiarrhythmic drugs and catheter ablation both to prevent VT or supraventricular tachycardia (SVT) and to control the ventricular rate in atrial fibrillation (AF) as well as the appropriate choice of hardware and device programming. This review focuses on ICD features and programming to minimize shocks.

Overview

Figure 1 summarizes the sequential processes required for an ICD to deliver a shock. The sense amplifiers convert the continuous electrogram (EGM) from the tip of the right ventricular (RV) lead into a series of instantaneously sensed events representing ventricular depolarization. This series of sensed events is processed by ICD algorithms, including those for initial detection; SVT-VT discrimination; and in some models of ICDs, enhancements to minimize oversensing. If the rhythm is classified as a VT, antitachycardia pacing (ATP) can be delivered. The ICD then performs a redetection process, which results in determination that the device-defined VT either has terminated or persists. If VT is redetected, the process iterates until all programmed ATPs are delivered. The ICD then charges the high-voltage capacitors, during which time a final round of ATP may be delivered. After capacitor charging, the ICD confirms that VT/VF is present before delivering a shock. Each step provides opportunities to minimize unnecessary shocks. Although Figure 1 shows the ICD process, we consider features and programming in the approximate order that most electrophysiologists program ICDs: (1) rate and duration for initial detection, (2) SVT-VT discrimination, (3) ATP and shock strength, (4) redetection/confirmation, and (5) sensing enhancements.

Historically, shocks were classified as appropriate if delivered during VT/VF and inappropriate if delivered during other rhythms. However, some shocks delivered during VT may be avoided by programming ATP or permitting nonsustained VT to spontaneously terminate. In this review, we classify shocks as either necessary to ensure patient safety or unnecessary. Necessary shocks are those that terminate ventricular tachyarrhythmias that would not spontaneously terminate or cannot be terminated by ATP. Unnecessary shocks include those that have been traditionally classified as inappropriate (shocks delivered for SVTs, oversensing) as well as those delivered for ventricular tachyarrhythmias (monomorphic or polymorphic) that would have spontaneously terminated without therapy delivery and VTs that would terminate with ATP or VT that is too slow to require therapy. The principal morbidity associated with ICD therapy is unnecessary shock delivery, which constitutes up to 50% of shocks in some clinical trials.

Rate (Interval) and Duration for Initial Detection

**Detection Rate (Interval)**

Shorter programmed cycle lengths for VT detection intervals reduce shocks, primarily from avoiding therapy for VT. The value of a shorter detection interval for SVT-VT discrimination is illustrated by the EMPIRIC (Comparison of Empiric to Physician-Tailored Programming of Implantable Cardioverter Defibrillators) trial, which compared empirical ICD programming using SVT-VT discriminators and ATP in all patients with physician-tailored programming. SVT-VT discriminators were programmed to be operational to an SVT limit of 300 ms in the empiric arm. In the tailored arm, SVT-VT discriminators and ATP were programmed inconsistently, but the mean tachycardia detection interval was shorter compared with empirical programming (350 versus...
400 ms). The shorter tachycardia detection intervals in the tailored arm did not result in statistically significant difference in either time to first shock for SVT or total number of shocks for SVT between the groups. In fact, the tailored arm fared better with regard to avoidance of inappropriate shocks in the initial duration of the follow-up, and the rates of inappropriate shock between groups converged only toward the end of the follow-up period.

ICD characterization of an interval as one that falls in the VT detection zone depends on the method of counting intervals. Most methods require that only 60% to 80% of consecutive intervals fulfill the interval criterion. The VT interval must be long enough to ensure detection of VT that can cause hemodynamic compromise. In primary prevention patients and patients whose only ventricular arrhythmia is VF, a sinus-VT/VF boundary in the range of 330 to 300 ms commonly is recommended. It rejects most sinus tachycardia in adults taking β-blockers yet rarely misses hemodynamically compromising VTs. In secondary prevention patients with monomorphic VT, the VT interval should be set with a safety margin at least 40 ms longer than the slowest VT.

**Duration**

The duration criterion is the time or number of intervals required to satisfy the rate criterion. A nominal value for VT or VF in Medtronic devices (12–18 beats) prevents therapy for nonsustained VT/VF. Two prospective randomized trials of primary prevention patients reported fewer shocks using a duration of 30 beats for VT/fast VT (FVT), with no increase in the incidence of syncope or death. An observational study of 88,000 primary and secondary prevention patients reported a monotonic reduction in the incidence of shocks as the number of intervals increased from 12 to 30. The mean and median time from detection to shock delivery for the subcutaneous ICD by Cameron Health are 13 and 14 s, respectively, whereas the 25% to 75% interval ranges from 13 to 16 seconds. The data regarding syncope with such relatively long detection to shock times are as yet unknown.

The effect of duration for the slower VT zone on shocks has not been studied systematically. However, even if ATP is programmed, a short duration for VT may increase the risk of inappropriate shocks for SVT that is not terminated by ventricular ATP. More consecutive intervals have a modest benefit in reducing unnecessary therapy of AF. It seems likely that durations of up to the 30 beats studied for FVT/VF should be safe and preferable, except possibly when consecutive-interval counting is used for irregular VTs.

**Detection of SVT**

Rapidly conducted AF and other SVTs account for nearly 80% of unnecessary shocks in patients with ICDs. All ICDs include algorithms to discriminate SVT and, thereby, withhold unnecessary therapy. These algorithms differ based on the presence or absence of an atrial lead.

**Discrimination Algorithms in Single-Chamber ICDs: Sudden Onset, Stability, and Morphology**

Significant overlap of SVT and VT rates has been reported in patients with secondary prevention ICDs and in those patients receiving antiarrhythmic drug therapy. These patients are...
those most likely to benefit from discrimination algorithms because lower programmed VT detection rates result in increased risk of unnecessary therapy for SVT.

Sudden onset that distinguishes VT from sinus tachycardia and the stability criterion that distinguishes VT from AF perform well at slower heart rates and should be programmed “on” in patients with slow VT zones.23 However, the performance of these criteria to distinguish sinus tachycardia and AF, respectively, from VT is limited to ventricular rates <180 to 190 beats/min in single-chamber (SC) ICDs,23 and the discriminatory capability of the stability criterion declines significantly at higher rates (>190 beats/min).24 Depending on the criterion, Swerdlow et al20 found that the accuracy of the Medtronic stability criterion degraded at 170 beats/min, depending on the duration required for detection.

In Medtronic dual-chamber (DC) ICDs, during a tachycardia, if either onset or stability is programmed on and indicates VT, the VT counter is reset to 0, detection is not met, and additional detection enhancements (PR Logic) are not applied. For this reason, onset is not routinely programmed on because sinus tachycardia also is distinguished from VT using PR Logic.13

High rate time out and sustained rate duration, although designed as a safety feature in the event that VT is misclassified as SVT, can be sources of unnecessary shocks because SVT episodes often last longer than the duration of the timer (nominally set at 3 minutes for Boston Scientific ICDs and 30 s for St Jude Medical ICDs). Further, in both the PREPARE (Primary Prevention Parameters Evaluation) and EMPIRIC studies, this safety feature was of little value, with no reported adverse events when it was programmed off.17 Medtronic, Biotronik, and the current generation of St Jude Medical ICDs (Accel and Fortify) have this feature nominally set off, whereas Sorin ICDs lack this algorithm.

Morphology discrimination (MD) compares the morphology of the EGM in sinus rhythm with the EGM during tachycardia. Various manufacturers’ proprietary algorithms differ in their EGM sources, methods of quantitative representation, and alignment. Rhythm identification using MD is predicated on the premise that the template sinus rhythm EGM (which must be updated periodically) is constant and the VT EGM is always significantly different from the template. Neither assumption is inadmissible. For example, morphology criteria fail to recognize rapid SVTs because of rate-related conduction abnormalities.25 Potential reasons for algorithm failure also include template misalignment, EGM maturation, postshock distortion, and pectoral myopotentials.26 The Rhythm ID algorithm (Guidant Corp) uses differences in the ventricular signal’s time of arrival at the rate-sensing and shock EGMs. The vector and timing correlation is the coefficient correlation between selected points on the rate-sensing EGM and the shock EGM. An initial study of the vector and timing correlation demonstrated 99% sensitivity and 97% specificity with single-chamber analysis.27 The Wavelet (Medtronic) is a morphology-based criterion that uses a template collected during sinus rhythm. The sinus template is compared with the ventricular EGM morphology during tachycardia. A match of ≥70% results in classification as SVT.25 The WAVE (Worldwide Application of Marquis VR Enhancements) study, evaluated this criterion’s ability to discriminate tachycardias. Unnecessary therapies for SVT were reduced by 78% for episodes within the range for which the criterion was programmed. Sensitivity for VT was 98.6%.28 In the REMEDIO (Spanish Register of Morphology Discrimination Criterion Wavelet) study, the accuracy of the Wavelet MD algorithm independent of other discrimination enhancements (rate onset and interval stability) was evaluated. Of the episodes of true VT/FVT, the sensitivity of the algorithm was 91.6%, and specificity was 90.6%. For VTs in the slowest analyzed range (cycle length, 340–500 ms), a specificity of 95.9% and a sensitivity of 83.2% were reported. It is important to point out that VT episodes classified as AF, where the lower sensitivity was identified, had a cycle length of >320 ms and never led to significant clinical consequences.28 In summary, MD is the single most effective SVT/VT discrimination enhancement in ICDs, especially in SC ICDs.

SC Versus DC ICDs

Historically, an argument for DC ICD implantation has been that the atrial lead adds valuable information for discrimination that is not available with SC algorithms and programming. Reliable atrial sensing is a prerequisite for accurate performance of discrimination algorithms in DC ICDs. Two frequent problems that may prevent accurate estimation of the atrial rate are atrial event undercounting because of prolonged or fixed atrial blanking periods and atrial event overcounting because of far-field R-wave sensing. Manufacturers have introduced several features to address these issues. St Jude Medical and Boston Scientific provide the option of reducing the duration of the programmable postventricular atrial blanking (PVAB) period, although this entails the risk of atrial rate overestimation because of oversensing far-field R waves. In Medtronic ICDs, the manufacturer-recommended PVAB operation maintains the integration of atrial sensing information during PVAB by the SVT/VT discrimination features to prevent atrial undercounting. The PR Logic algorithm rejects far-field R waves when there is a 2:1 AV rhythm with a consistent short-long pattern of atrial-sensed events combined with a PR interval (atrial-sensed event to the next ventricular-sensed event) <60 ms or an RP interval (ventricular-sensed event to the next atrial-sensed event) <160 ms. The PARAD (ELA/Sorin) algorithm also uses an analogous scheme and excludes intervals shorter than a predetermined value to reject far-field R waves.

DC ICDs should have superior arrhythmia discrimination capabilities if atrial EGMs are identified correctly. However, multiple studies have failed to show conclusive superiority of DC devices over SC ICDs in reducing unnecessary shocks (Table 1). In most studies, discrimination of SVT with a fixed N:1 AV conduction pattern was suboptimal in both SC and DC devices. There are a number of reasons for failure of DC discrimination in reducing unnecessary shocks in such patients. First, a progressively prolonging AV interval can be misclassified as VT with retrograde conduction. This problem has been reported as the most common reason for failure of the PR Logic algorithm before inclusion of MD.13,35 Second, in cases of
ventricular premature beats during sinus tachycardia, the DC detection enhancement "ventricular rate > atrial rate" criterion can accelerate inappropriate detection because of the postventricular atrial blanking after a sensed ventricular event. Frequent premature ventricular contractions also may result in the inappropriate calculation of a sudden onset.35 Third, the performance of various discrimination algorithms also is less than optimal for AF with rapid ventricular response.35,37 Fourth, fortuitously greater use of ATP in SC devices could have prevented shocks for inappropriate detections by terminating AV node-dependent SVTs, delaying shocks long enough to permit spontaneous slowing or termination of SVT and slowing of SVTs by concealed retrograde penetration of the AV node.32

Atrial leads with interelectrode spacing ≤10 mm minimize far-field R-wave sensing. Preliminary data from an atrial lead with a 1.1-mm interelectrode distance support this concept.38,39 The addition of an atrial lead purely for discrimination purposes is accompanied by increased procedural times and increased risk of lead dislodgement that necessitates surgical revision. This has prompted investigation of ICDs using a single lead that have a noncontact atrial sensing bipolar integrated into the ICD lead. The recently published ADRIA (Study to Verify Proper Detection of Supraventricular Tachyarrhythmias With Single-Lead Dual-Chamber Implantable Cardioverter-Defibrillators) study, however, failed to show noninferiority of such a system to traditional DC ICDs in the discrimination of SVTs and VT.40 Furthermore, there was a high incidence of atrial undersensing and far-field R-wave sensing with this lead.

### Table 1. Studies Evaluating Single- Versus Dual-Chamber ICDs

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>No. of Patients</th>
<th>Discriminators Used</th>
<th>Findings</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Kuhlkamp et al (1999)29</td>
<td>94</td>
<td>1. Onset</td>
<td>Eight of 39 patients in the DC group and 7 of 55 in the SC group received inappropriate therapy. In the SC group, of all the AF/flutter episodes, 24% were treated inappropriately vs 41% in the DC group (P&lt;0.1).</td>
<td>Atrial undersensing, especially in the setting of 2:1 AV relationship of the tachycardia, resulted in higher rates of inappropriate therapy in the DC group.</td>
</tr>
<tr>
<td>Deisenhofer et al (2001)30</td>
<td>92</td>
<td>1. Onset</td>
<td>Six of 45 patients in the SC group and 10 of 47 in the DC group had inappropriate therapies (P NS).</td>
<td>Thirty-two of 51 inappropriate detections in the DC group resulted from intermittent atrial sensing problems that led to failure of the respective DC algorithms.</td>
</tr>
<tr>
<td>PINAPPs31</td>
<td>60</td>
<td>1. V → A</td>
<td>Seven of 31 patients in the DC group received inappropriate therapy vs 6 of 29 in the SC group.</td>
<td>The applied detection criteria in DC devices did not offer benefits in the rejection of SVTs. DC devices had problems in discriminating SVTs with a stable AV relationship.</td>
</tr>
<tr>
<td>1+1 Trial (2004)32</td>
<td>102</td>
<td>1. Onset</td>
<td>Sensitivity was 0.94 in the DC mode and 0.82 in the SC mode (P=0.1345). The specificity was 0.81 in the SC mode and 0.93 in the DC mode.</td>
<td>DC detection with a long TDI might improve VT detection with high specificity, especially in patients with slower VTs.</td>
</tr>
<tr>
<td>DETECT SVT (2006)33</td>
<td>400</td>
<td>1. Rate branch</td>
<td>Inappropriate detection of SVT was 46.5% in the SC group vs 32.3% in the DC group. DC group had a reduction in inappropriate detection by almost 50% (OR, 0.53; P=0.03). Inappropriate therapy delivery (ATP/shock) was 38.3% in the SC group vs 26.1% in the DC group (P=0.02).</td>
<td>No statistically significant reduction in inappropriate shocks in the DC group despite a reduction in misclassification of SVTs as VT.</td>
</tr>
<tr>
<td>DATAS (2008)34</td>
<td>334</td>
<td>1. Stability</td>
<td>Three of 112 patients in the DC mode vs 20 of 222 patients in SC mode received inappropriate shocks.</td>
<td>Inappropriate shocks were part of a composite score, and the ability of SC and DC modes for appropriate discrimination and therapy delivery was not the primary end point evaluated. Signal was toward decreased number of inappropriate shocks in the DC mode.</td>
</tr>
</tbody>
</table>

A indicates atrial; AF, atrial fibrillation; ATP, antitachycardia pacing; DATAS, Dual Chamber and Atrial Tachyarrhythmias Adverse Events Study; DC, dual chamber; DETECT SVT, Detect Supraventricular Tachycardia study; ICD, implantable cardioverter-defibrillator; MD, morphology discrimination; NS, not significant; OR, odds ratio; PINAPPs, Prevention of Inappropriate Therapy study; SC, single chamber; SVT, supraventricular tachycardia; TDI, tachycardia detection interval; V, ventricular; VT, ventricular tachycardia.
Therapy and Therapy-Zone Boundaries

Antitachycardia Pacing

ATP reduces shocks delivered for both VT and SVT.\(^9,14,17,41\) Initially, ATP was limited to slower VTs. After analysis of ICD-stored EGMs demonstrated that monomorphic FVT was the most common tachyarrhythmia in ICD patients without a history of clinical VT,\(^42\) studies established that ATP terminates many spontaneous FVTs\(^9,14,17,41,43\) (Figure 2) and that syncope after unsuccessful ATP is rare in modern ICDs with short charge times.\(^35\) Today, ATP is the primary therapy delivered by ICDs.

Despite its unquestioned success at reducing shocks, it is difficult to assess efficacy of ATP accurately. Delivering ATP after short durations of VT overestimates efficacy because many short episodes terminate spontaneously.\(^14,19\) For example, ATP “terminates” \(\approx 90\%\) of FVT (\(< 330\) ms) when duration is programmed to 12 beats\(^8\) but only 50% when duration is programmed to 30 beats.\(^35\)

Multiple factors may affect the efficacy of ATP,\(^42\) and their relative contribution is difficult to assess. A randomized controlled trial reported that for FVT, adaptive burst pacing at 88% of the VT cycle length was more effective than ramp pacing and caused less acceleration.\(^44\) Generally, shorter adaptive burst cycle lengths of 75% to 84% are required for slower VTs. In patients receiving cardiac resynchronization therapy, left ventricular (LV) or biventricular ATP may improve efficacy.\(^45\) Analysis of the return cycle after unsuccessful ATP may permit tuning ATP. If the VT is not reset, ATP stimuli have not reached the reentry circuit; adding stimuli may improve efficacy by “peeling back refractoriness” between the pacing site and reentry circuit. If the circuit is reset, ATP pulses traverse the circuit orthodromically without causing bidirectional block. Addition of a premature stimulus at the end of the pacing train (“burst +” mode) may be effective.

ATP during charging reduces the time from ATP to shock if ATP fails to terminate VT, but it has 2 limitations. First, ATP during charging causes battery depletion equivalent to a shock. Second, because shock confirmation after charging is less specific than the VT redetection after ATP, shocks are delivered after \(\approx 5\%\) of successful ATP sequences.\(^46,47\) We believe that programming appropriate rate zones and different therapies for slow and faster ventricular arrhythmias would provide similar clinical benefit as ATP during charging. Nevertheless, if one decides to program ATP before shock delivery in faster

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Figure 2. Results of the PainFree Rx II (Pacing Fast Ventricular Tachycardia Reduces Shock Therapies) trial.\(^41\) The pie charts show terminating therapy for FVT episodes in each arm. Percentages are adjusted by generalized estimating equations. The bar graph shows distribution of ventricular arrhythmias by detection zone and median cycle length. In conventional implantable cardioverter-defibrillator programming, all episodes \(< 320\) ms (VF and FVT in pie chart) would be detected as VF and shocked without ever attempting ATP. Note that FVT episodes represent 76% of these rhythms. ATP indicates antitachycardia pacing; FVT, fast ventricular tachycardia. Other abbreviations as in Figure 1.
ventricular tachyarrhythmias, the Charge Saver feature would prevent battery depletion and allow the device to switch from ATP during charging to ATP before charging, which necessitates reconfirmation of ventricular tachyarrhythmias after delivery of 1 sequence of ATP by the ICD.

**Therapy-Zone Boundaries**

ATP programming is the key determinant of zone boundaries for ventricular therapy. Some ICDs limit the use of SVT discriminators in faster (FVT and VF) zones. In 3-zone programming, the boundary between the 2 VT zones should be based on the cycle length at which different adaptive burst cycle lengths or fewer trials of ATP are preferred. Limited data indicate that 2 trials of ATP terminate \( \approx 90\% \) of all episodes terminated by ATP.\(^{14} \) The VT-VF boundary is based on the cycle length below which ATP or ATP before charging should not be delivered.

**Shock Strength**

In adults, shocks for VF are routinely programmed either to energy outputs 10 J higher than the defibrillation threshold determined during implant testing or to maximal output by the majority of practitioners. Although monomorphic VTs often can be terminated by low-energy cardioversion, low-energy shocks risk accelerating VT to VF. Further, if rapidly conducted AF is detected inappropriately as VT, there is a good chance of terminating AF with a strong shock (especially with a dual-coil ICD lead) but little chance with a weak shock. Because delays in charging are less significant during VT than VF and shock pain is (practically speaking) independent of shock strength, we recommend programming VT shocks at least as strong as the first VF shock to minimize the number of shocks.

**Redetection, Confirmation, and Episode Termination**

Redetection is the process by which ICDs determine whether VT or VF detection criteria remain satisfied after therapy. The duration for redetection is programmable independently of the duration for initial detection and typically is shorter than that for initial detection. Longer redetection durations may be advisable if ATP results in type 2 breaks with transient acceleration before termination. ICD-defined arrhythmia episodes continue after each therapy until either VT/VF is redetected or the rhythm is classified as normal (sinus), resulting in episode termination. Typically, episode termination depends on (slow) rate and duration, with 3 to 8 beats classified as sinus. The number of intervals required for episode termination is programmable in St Jude Medical ICDs (3, 5, or 7). Reduction in the number of intervals for redetection will minimize the overall duration of episodes. Such programming is advisable when ATP terminates VT, but sustained VT reinitiates promptly after termination. This permits repeating the first sequence of programmed ATP before delivering more-aggressive therapies as the ICD considers the reinitiated VT as a de novo VT. Such programming could be of benefit in patients with intractable VT awaiting heart transplantation with or without an LV assist device.

Confirmation or reconfirmation is the process that occurs after charging by which ICDs determine whether to deliver or abort the first shock in a sequence. ICDs deliver the stored shock if a few intervals immediately after charge completion are shorter than the programmed VT interval (St Jude Medical, Boston Scientific, Sorin, Biotronik) or are within 60 ms of the VT interval (Medtronic ICDs before the Protecta family). Thus, in some ICDs, the first VF shock is effectively committed if the VT interval (or, in some ICDs, the monitor-only interval) is programmed to a long cycle length.\(^{48,49} \) A new shock confirmation algorithm in Medtronic ICDs (Protecta family) is designed to prevent shocks for post-VT sinus tachycardia. It aborts a shock for a regular VT if the cycle length increases by at least 60 ms relative to the detected regular tachycardia and exceeds the VF detection interval.

**Features To Optimize Sensing**

**T-Wave Oversensing**

T-wave oversensing (TWOS) can cause spurious ICD detections and unnecessary therapy. It is relatively more common when the measured R waves are of low amplitude (<3 mV) and, at least for older ICDs, with specific ICD lead types and devices. Hypertrophic cardiomyopathy with resultant high-amplitude T waves, short- and long-QT syndromes, Brugada syndrome, and various channelopathies may be associated with higher incidences of TWOS. The following sections discuss strategies to overcome TWOS.

**Decreasing the Sensitivity**

Such an intervention is predicated on R waves of adequate amplitude. St Jude Medical devices allow programming of separate maximum sensitivity settings for the pacer and defibrillator functions.

**Programming Decay in Sensitivity**

St Jude Medical and Biotronik devices have the option of altering the initial value, onset time, and slope of the automatically adjusting sensitivity algorithm after a sensed QRS. These features can be particularly useful in patients with long-QT syndrome.\(^{50} \) In St Jude Medical ICDs, the algorithm integrates the QRS signal and starts a sensing decay from a programmable threshold start value (nominal 62.5\% of the maximal amplitude of the R wave, resulting during the refractory period, until 100\% of the maximal R-wave amplitude). The subsequent decay is linear, and the sensitivity is increased by 1 mV every 312 ms. The decay delay is programmable from 0 to 220 ms. The enhanced T-wave suppression setting in Biotronik devices uses increased high-pass filtering and modification of upper-ceiling thresholds for R-wave sensitivity to eliminate TWOS.

The latest generation of Medtronic ICDs (Protecta) incorporates a TWOS algorithm that operates on the assumption that R and T waves have different waveform characteristics and frequencies of the RV-sensed EGM (RV\(_{\text{up-ring}}\) or RV\(_{\text{up-coil}}\)). Outputs from the standard sense amplifier are compared with those of the same signal passed through an additional differential, high-pass filter. The latter reduces the amplitude of low-frequency T waves with minimal reduction in R-wave amplitude. Identified R and T waves must fulfill several criteria to be confirmed as a consistent TWOS pattern. These
include R- and T-wave amplitude stability, R-T pattern, and interval stability as well as the true R-R intervals being longer than the slowest programmed detection zone. The advantage of this approach is that it does not reduce sensitivity for VF. This algorithm is operational even during redetection. Additionally, the Protecta and earlier generations of ICDs from Medtronic have a programmable RV-sensing vector to either true bipolar or integrated bipolar sensing.

Lead Fracture Surveillance

One of the most important and common causes of oversensing and resultant unnecessary shocks is ICD lead failure. It has become a subject of intense focus after Medtronic voluntarily discontinued sale of the Sprint Fidelis ICD lead in 2007. Prompt diagnosis of lead failure, reduction of unnecessary shocks, and alerting the patient and physician can be achieved by a combination of Lead Integrity Alert (LIA) and Lead Noise Oversensing Algorithms in Medtronic ICDs.

The low sensitivity of the traditional method of detecting lead failure by fixed thresholds for abnormal impedances led to the development of the LIA based on work over the past decade analyzing changes in lead impedance and oversensing over time from stored device diagnostics. These diagnostics were then tested in large databases of patients with implanted devices with and without lead failure. The latest iteration of the LIA is triggered if 2 of the following 3 criteria are met: (1) abnormal change in RV lead impedance, (2) ≥2 high-rate nonsustained VTs (=5 beats) with V-V intervals <220 ms (nonsustained tachycardia), or (3) at least 30 short V-V interval counts (sensing integrity counter [SIC]) within 3 consecutive days. Using SIC alone as a marker of nonphysiological oversensing resulting from lead/connector problems that require surgical intervention will result in a significant number of false positives. An elevated SIC alone is more often due to physiological oversensing (diaphragmatic myopotential oversensing and P-, R-, or T-wave double-counting) than lead/connector problems. Thus, a patient with an elevated SIC alone requires a careful review of data to determine the cause of the SIC.

Increased SIC and the additional finding of rapid nonsustained tachycardias usually indicate a high specificity and moderate sensitivity a lead/connection issue, even in the absence of impedance abnormalities. The LIA has been validated to provide timely warning of unnecessary shocks and to prevent unnecessary shocks, both retrospectively and prospectively. A recent study focused on the behavior of impedance changes to discriminate fractures from other causes of high impedance and nonphysiological noise oversensing. Swerdlov et al. showed that extremely high maximum impedance or noise oversensing with a normal impedance trend indicates a fracture, whereas a short interval from surgery to impedance rise or prolonged stable impedance after an abrupt rise indicates a connection problem. A gradual impedance increase or stable high impedance indicated a clinically functioning lead. A flow chart using short R-R intervals and other ICD diagnostics to determine the likelihood of a lead fracture/connection issue is presented in Figure 4.

Newer lead noise oversensing algorithms analyze the far-field EGM (RV_{tip-ring}, SVC or Can-RV_{coil}) in an amplitude measurement window centered around each event sensed on the near-field EGM (RV_{tip-ring} or RV_{tip-coil}). Oversensing because of a lead or connection problem is identified when the peak-to-peak amplitudes seen on the far-field signal have a large disparity, indicating that these amplitude measurement windows are sensing both R waves and absence of R-waves (isoelectric potentials). Retrospective testing of this algorithm yielded promising results and is incorporated in the Protecta family of ICDs by Medtronic.

Electromagnetic Interference Rejection Algorithms

The most frequent response to electromagnetic interference (EMI) in patients with ICDs is spurious ICD tachyarrhythmia detection. Noise-protection algorithms, which are based on the fact that rapid-sensed signals with intervals shorter than a threshold value are unlikely to represent myocardial activation, are designed to overcome EMI. However, they are more difficult to implement in ICDs than in pacemakers because ICDs must be able to recognize the rapid rates of VF. Therefore, long blanking periods after sensed events are not feasible. Lead problems causing oversensing typically are isolated to the near-field sensing signal in contrast to EMI, which can result in oversensing on all channels, albeit to a lesser extent in the near-field true bipolar sensing signal. The Dynamic Noise Algorithm in newer Boston Scientific devices (Teligen, Cognis) uses characteristics of the sensed signal, which include frequency and an approximation to the noise power, to identify a signal as noise and then separates sensing frequency range into a lower band and an upper band. It then evaluates the upper band for noise (noise tends to be higher frequency). When the algorithm determines that noise is present, it raises a dynamic sensing floor above the noise amplitude. It is automatically active on all sensing channels (atrium, RV, and LV) and keeps the floor above the noise, helping to prevent oversensing. There are no markers related to the use of the Dynamic Noise Algorithm when it is operational. Even though this algorithm was designed to minimize the risk of diaphragmatic myopotential oversensing, we have observed episodes of accurate rejection of EMI by the algorithm. There is no information on how this algorithm performs with lead or insulation failure. Sorin devices (Ovatio, Paradym) also decrease sensitivity if noise is detected (signals sensed >16 Hz). ICDs from Boston Scientific, Sorin, and St Jude Medical provide programmable noise-reversion modes, but their performance against common sources of EMI has not been reported. Medtronic ICDs lack noise-reversion capabilities.

Physiological Oversensing

Other causes of unnecessary therapies have been reported, including oversensing of diaphragmatic myopotentials and double counting of R or P waves. Myopotential oversensing with complete heart block is an exception to the rule that syncope before a shock indicates a necessary shock. It is most common in male patients who have integrated bipolar leads in the RV apex with Boston Scientific ICDs that use Automatic Gain Control before Boston Scientific incorporated a noise-rejection algorithm. R-wave double-counting
was more common in the earliest generation of CRT defibrillators (CRT-Ds) that sensed from the composite RV-LV EGM. Sporadic, asymptomatic R-wave double-counting (related to premature ventricular contractions) also is reportedly more common with integrated bipolar leads than with true bipolar leads.\(^{52}\) It is rarely seen in current generations of ICDs and CRT-Ds. A common cause of clinically significant R-wave double-counting in CRT-Ds is loss of RV capture. In Biotronik ICDs, R-wave double-counting of spontaneous R waves has been reported if integrated bipolar leads are used for ventricular sensing.\(^{56}\) This particular problem has been attributed to the short, nominal, postventricular sense blanking periods of these devices. This problem has been successfully resolved by prolonging the ventricular postsense blanking period and by reprogramming the rectification settings in Biotronik ICDs.\(^{57}\)

### Special Considerations

**ICD Proarrhythmia**

The most common cause of ICD proarrhythmia, barring mechanical issues with the ICD lead, is the pacing function of an ICD. Proposed mechanisms for pacing-induced VT/VF induction by the ICDs are short-long-short (S-L-S) sequences that are either pacing facilitated or pacing permitted,\(^{57}\) atrial preference pacing,\(^{58}\) and noncompetitive atrial pacing mode.\(^{59}\) When the paced QRS morphology and VT morphology are similar, one should consider mechanical irritation from the lead as a potential mechanism of VT.\(^{60}\) Studies aimed at reducing S-L-S sequences by using rate-smoothing algorithms have not shown consistent benefit.\(^{61,63}\) Occasionally, pacing-facilitated S-L-S VT can be due to Wenckebach upper rate response, which
results in varying sensed AV interval, upper rate ventricular pacing, and periodic abrupt increases in ventricular paced intervals (pauses). To suppress Wenckebach upper rate behavior, upper tracking rates can be increased and postventricular atrial refractory period (PVARP) reduced. Automatic PVARP, which determines a value for PVARP based on the mean sensed atrial rate, is intended to maintain 1:1 AV synchrony at high sinus rates and suppress Wenckebach and 2:1 upper rate behavior by shortening PVARP while protecting against endless loop tachycardias at lower rates by lengthening PVARP.64

**Programming During Electrical Storm**

Electrical storm in patients with ICDs has been defined as ≥3 true VT/VF therapies in 24 hours.65 It is associated with a poor prognosis and causes psychological trauma to patients and families. In some patients, overdrive pacing by increasing the lower pacing rate of the ICD may suppress electrical storm, particularly if DC pacing is available. ICD programming should focus on minimizing shocks. Safety features that apply a shock after a programmable time window independent from programming of ATP should be prolonged or disabled. In those instances in which safety features have been disabled, commanded shocks after the patient has lost consciousness reduce the psychological trauma and sympathetic overdrive associated with repetitive shocks. In most patients, the number of VT cycles or duration necessary for detection can be increased significantly, thus allowing for spontaneous termination of nonsustained VT. Similarly, criteria for redetection can be prolonged to reduce the risk of inappropriate detection of (repetitive) nonsustained VT in many patients. Radiofrequency ablation might be the only option in the treatment of electrical storm refractory to amiodarone and sympathetic blockade.

**Device Therapy for AF**

Mechanisms by which AF leads to VT/VF are (1) direct causation, where a rapid ventricular rate during an atrial tachyarrhythmia directly reduces ventricular refractoriness, and (2) indirect causation, where irregular rhythm of AF leads to S-L-S sequences that may be intrinsically proarrhythmic. An analysis of device-stored EGMs revealed that 50% of ventricular arrhythmic episodes are preceded S-L-S cycles in patients with a history of persistent AF.66 Moreover, rapidly conducted AF can result in unnecessary ventricular therapies if ventricular rate criteria are fulfilled. DC ICDs capable of delivering tiered atrial therapies for AT/AF treatment, which include atrial ATP, high-frequency (50 Hz) burst pacing, and atrial defibrillation, have not shown a significant reduction in the incidence of VT/VF.67 It might be overly simplistic to assume that device-based therapy to maintain sinus rhythm in patients with AF would prevent the clinical milieu that would cause VT/VF. Adequate ventricular rate control is more beneficial in reducing delivery of unnecessary shocks than atrial-based therapies in ICD patients with AF.

**Pediatric Patients**

Because median-detected VT rates in the more common congenital heart diseases such as transposition of great arteries and tetralogy of Fallot are 213 and 222 beats/min, respectively, programming a single VF zone at >200 beats/min is probably reasonable in primary prevention patients.68–70 The programming recommendations for secondary prevention patients essentially are the same as those for adults. Certain subsets of pediatric patients warrant additional ICD programming. In patients with congenital heart block, discriminators should be turned off because rapidly conducted SVT is a nonissue. In other patients, SVT discriminators, however, should be programmed up to 200 beats/min, which is the programmable upper rate limit for discriminators in Medtronic and St Jude Medical devices. In Biotronik and Boston Scientific devices, the upper limit of discriminators is linked to the rate of programmed VT-1 and VT-2 zones and, therefore, does not overlap with VF zones. Rate smoothing

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**Figure 4.** Flowchart using short R-R intervals and other implantable cardioverter-defibrillator diagnostics to determine the likelihood of lead fracture/connection issue. The diagnostics include SIC, NST, Z, and EGM. EGM indicates electrograms; NST, nonsustained tachycardia; SIC, sensing integrity counter; V, ventricular; Z, impedance trend. Reproduced with permission from Swerdlow CD et al.54

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may be programmed on in patients with long-QT syndrome or demonstrated VT triggered by S-L-S sequences. If programmed, a value of 12% (which defines the maximum degree to which intervals may vary) is recommended. The role of ATP in pediatric ICDs is controversial. In a recent long-term observational study of patients 6 to 21 years of age with ICDs, ATP did not reduce shocks.71 However, we and others70 recommend that ATP should be programmed in secondary prevention patients. Finally, because TWOS is a common occurrence in pediatric patients with hypertrophic

Table 2. Ongoing Clinical Trials

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Estimated Enrollment, n</th>
<th>Study Start Date</th>
<th>Estimated Completion Date</th>
<th>Aim</th>
<th>Primary End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Use of Dual Chamber ICD With Special Programmed Features to Lower the Risk of Inappropriate Shock (RAPTURE)—NCT00787800</td>
<td>100</td>
<td>11/2008</td>
<td>12/2011</td>
<td>Whether DC ICDs with atrial prevention and termination therapies, minimized ventricular pacing, and remote monitoring will reduce the rate of inappropriate shocks and improve quality of life compared with optimally programmed backup pacing-only SC ICDs when used for primary prevention of sudden cardiac death.</td>
<td>Rate of inappropriate shocks (time frame, 12 mo).</td>
</tr>
<tr>
<td>Avoid Delivering Therapies for Non-sustained Arrhythmias in ICD Patients III (ADVANCEIII)—NCT00617175</td>
<td>1835</td>
<td>3/2008</td>
<td>12/2011</td>
<td>To demonstrate a reduction in the number of ventricular therapies (ATP and shocks) delivered for treating spontaneous arrhythmia episodes with a fast cycle length (≤320 ms) as a consequence of self-termination and better arrhythmia discrimination because of a greater NID (30/40).</td>
<td>Demonstrate a 20% reduction of ventricular therapies (ATP and shocks) delivered for treating spontaneous arrhythmia episodes with a fast cycle length (≤320 ms) with strategic programming.</td>
</tr>
<tr>
<td>Efficacy of the ATP Autoswitch Automatic Programming in Implantable Cardioverter Defibrillator (ICD) and Cardiac Resynchronization Therapy Defibrillator (CRT-D) Implanted Patients (ASAP)—NCT01169246</td>
<td>1775</td>
<td>11/2009</td>
<td>11/2013</td>
<td>Primary objective is to assess the efficacy of the new ATP Autoswitch function.</td>
<td>Ventricular arrhythmia reduction.</td>
</tr>
<tr>
<td>Termination of Fast Ventricular Tachycardia Episodes by the Antitachycardia Pacing Algorithm “ATP One Shot” (Favorite ATP)—NCT00617578</td>
<td>200</td>
<td>11/2007</td>
<td>12/2012</td>
<td>Evaluate the efficacy of the ATP One Shot algorithm for the termination of FVT episodes. Spontaneous episodes detected in the VF zone of the ICD will be evaluated with regard to cycle length, episode duration, and course of device therapy.</td>
<td>Time to the first adequate ICD shock.</td>
</tr>
<tr>
<td>Optimal Anti-tachycardia Therapy in Implantable Cardioverter-defibrillator (ICD) Patients Without Pacing Indications (OPTION)—NCT00729703</td>
<td>461</td>
<td>6/2006</td>
<td>7/2011</td>
<td>Impact of a new pacing mode avoiding unnecessary ventricular stimulation in combination with advanced DC detection with slow VT management on the clinical outcome for hospitalization and mortality and inadequate therapy in medically stable, ICD-indicated patients with LVEF =40% who do not have pacing indications and no indication for CRT.</td>
<td>The first part is the time to first occurrence of inappropriate ICD shock therapy. The second part is the composite end point of time to first occurrence of death (all causes) or hospitalizations because of a cardiovascular event.</td>
</tr>
<tr>
<td>Multicenter Automatic Defibrillator Implantation Trial—Reduce Inappropriate Therapy (MADIT-RIT)—NCT00947310</td>
<td>1500</td>
<td>9/2009</td>
<td>9/2011</td>
<td>Compare the time to first inappropriate therapy using high-rate cutoff and long delay in primary prevention patients receiving an ICD or CRT-D device compared to standard programming.</td>
<td>Time to first inappropriate therapy. Secondary outcome measures include all-cause mortality and syncope.</td>
</tr>
<tr>
<td>The PainFree SST Clinical Study—NCT00962397</td>
<td>2000</td>
<td>9/2009</td>
<td>5/2013</td>
<td>The inappropriate shock-free rate at 1 year of subjects implanted with a Medtronic Protecta ICD and CRT-D will be evaluated.</td>
<td>Evaluate reduction of inappropriate and unnecessary shocks from time of implant to 1-year postimplant. Additional objectives include safety of extending NID from 18 of 24 to 30 of 40 intervals.</td>
</tr>
</tbody>
</table>

CRT-D indicates cardiac resynchronization therapy defibrillation; FVT, fast ventricular tachycardia; LVEF, left ventricular ejection fraction; NID, number of intervals needed for detection; VF, ventricular fibrillation. Other abbreviations as in Table 1. 

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Table 3. Suggested Programming for Specific ICD Indications

<table>
<thead>
<tr>
<th>Condition</th>
<th>Arrhythmia Features</th>
<th>Programming</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary prevention (low EF)</td>
<td>FVT often is monomorphic and heart rate is &gt;200 beats/min</td>
<td>Use 2 detection zones with VT cutoff of 180–190 beats/min. Use 1–2 sequences of ATP for tachycardias &lt;250 beats/min.</td>
<td>Detection algorithms are not exposed to lower rates, thus minimizing inappropriate detections. Two zones permit increased ATP use in the lower heart rate zone.</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>Monomorphic VT with heart rates 120–200 beats/min</td>
<td>Program detection enhancements on; use DC enhancements if available.</td>
<td>Permits increased detection enhancements and ATP for slow VTs. Permits tiered therapies. ATP could terminate SVT and VT, thus reducing the risk of shock therapy.</td>
</tr>
<tr>
<td></td>
<td>FVT/VF often monomorphic, heart rate &gt;200 beats/min</td>
<td>Multiple sequences of ATP in slower zones; 1–2 sequences for heart rates between 200 and 250 beats/min.</td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Bradycardia VT/VF</td>
<td>Avoid RV pacing and use RV pacing avoidance algorithms if available. Program as for primary and secondary prevention.</td>
<td>Chronic RV pacing may exacerbate heart failure. Attrial termination algorithms may be particularly useful in patients with atrial flutter and other atrial tachycardias. Avoid use in first month because of potential for lead dislodgement. Avoid shocks for atrial arrhythmias.</td>
</tr>
<tr>
<td>History or risk of rapidly conducting AF</td>
<td>AF Sinus bradycardia</td>
<td>Promote atrial pacing and minimize ventricular pacing. SVT discriminators such as interval stability and morphology.</td>
<td></td>
</tr>
<tr>
<td>Channelopathies</td>
<td>Rapid polymorphic VT/VF Frequent nonsustained episodes</td>
<td>Single detection zone for heart rates &gt;200 beats/min. Detection enhancements off. Avoid ATP Prolong detection Screen for TWOS and program as necessary</td>
<td>Clinical arrhythmia is rapid, thus underdetection of slower rhythms is not a concern; young patients can achieve physiologically rapid heart rates with exercise. Enhancements generally are ineffective in VF zone at rapid rates. Role of ATP in polymorphic VT/VF is not established; ATP could be proarrhythmic. Prevents unnecessary charging and shocks. Prevents inappropriate shocks.</td>
</tr>
<tr>
<td></td>
<td>Brugada and long QT during sinus rhythm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RV indicates right ventricular; TWOS, T-wave oversensing. Other abbreviations as in Tables 1 and 2.

cardioomyopathy and long-QT syndrome, it would seem prudent to implant ICDs with programming options to prevent TWOS in these conditions.

Remote Monitoring

Wireless remote monitoring with automatic clinician alerts have improved our ability to collect and clinically integrate the information gleaned from ICD diagnostics over extended periods of time. The TRUST (Lumos-T Safely Reduces Routine Office Device Follow-up) and CONNECT (Clinical Evaluation of Remote Notification to Reduce Time to Clinical Decision) studies have demonstrated that timely alerts from remote monitoring reduce the time between onset of clinically significant events and subsequent clinician action to address these events. Remote monitoring provides opportunities for clinical intervention, often weeks in advance; however, to date, no study has demonstrated shock reduction by remote monitoring compared with standard programming.

Future Directions

Present clinical trials focusing on shock reduction include novel ATP strategies, discrimination algorithms, and increased detection durations. These are cited in Table 2, and suggested programming parameters are provided in Table 3.

Disclosures

Dr Koneru has scholarship support from Medtronic and is a member of the Fellows’ Advisory Board for Medtronic. Dr Swerdlow is a consultant and receives honoraria from Medtronic and St Jude Medical. Dr Wood is a consultant and receives honoraria from Medtronic, Boston Science, and Biotronik. He also receives research grants from Medtronic and St Jude Medical and fellowship support from Medtronic and Boston Scientific. Dr Ellenbogen is a consultant and receives honoraria from Biotronik, Boston Scientific, and Medtronic. He also receives research grants from Medtronic, St Jude Medical, and Boston Scientific as well as fellowship support from Medtronic and Boston Scientific.

References


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20. Swerdlow CD, Chen PS, Kass RM, Allard JR, Peter CT. Discrimination
19. Swerdlow CD, Shehata M. Antitachycardia pacing in primary-prevention
18. Saeed M, Neason CG, Razavi M, Chandiramani S, Alonso J, Natarajan S,
17. Russo AM, Nayak H, Verdino R, Springman J, Gerstenfeld E, Hsia H,
13. Friedman PA, McClelland RL, Bamlet WR, Acosta H, Kessler D, Munger
11. van Rees JB, Borleffs CJ, de Bie MK, Stijnen T, van Erven L, Bax JJ,
10. Swerdlow CD, Brown ML, Lurie K, Zhang J, Wood NM, Olson WH,
8. Saeed M, Neason CG, Razavi M, Chandiramani S, Alonso J, Natarajan S,
7. Levy WC, Lee KL, Hellkamp AS, Poole JE, Mozaffarian D, Linker DT,
6. Sweeney MO, Sherfesee L, DeGroot PJ, Wathen MS, Wilkoff BL. Differ-
5. Swerdlow CD, Brown ML, Lurie K, Zhang J, Wood NM, Olson WH,
3. Asirvatham SJ, Bruce CJ, Danielens A, Johnson SB, Okumura Y,
1. Koneru et al Appropriate Programming of ICDs

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23. Brugada J, Mont L, Figueiredo M, Valentino M, Matas M, Navarro-Lopez P. Enhanced detection criteria in implantable defibril-
20. Swerdlow CD, Brown ML, Lurie K, Zhang J, Wood NM, Olson WH, Gillberg JM. Discrimination of ventricular tachycardia from supraven-
11. Kuhlkamp V, Dornberger V, Mewis C, Suchalla R, Bosch RF, Seipel L. Clinical experience with the new detection algorithms for atrial fibrilla-
10. Swerdlow CD, Brown ML, Lurie K, Zhang J, Wood NM, Olson WH, Gillberg JM. Discrimination of ventricular tachycardia from supraven-
6. Sweeney MO, Sherfesee L, DeGroot PJ, Wathen MS, Wilkoff BL. Differ-
5. Swerdlow CD, Brown ML, Lurie K, Zhang J, Wood NM, Olson WH, Gillberg JM. Discrimination of ventricular tachycardia from supraven-
3. Asirvatham SJ, Bruce CJ, Danielens A, Johnson SB, Okumura Y, Kathmann E, Packer DL, Friedman PA. Intramyocardial pacing and
1. Koneru et al Appropriate Programming of ICDs

6. Sweeney MO, Sherfesee L, DeGroot PJ, Wathen MS, Wilkoff BL. Differ-
5. Swerdlow CD, Brown ML, Lurie K, Zhang J, Wood NM, Olson WH,
3. Asirvatham SJ, Bruce CJ, Danielens A, Johnson SB, Okumura Y, Kathmann E, Packer DL, Friedman PA. Intramyocardial pacing and
23. Brugada J, Mont L, Figueiredo M, Valentino M, Matas M, Navarro-Lopez P. Enhanced detection criteria in implantable defibril-
sensing for the enhancement of cardiac stimulation and sensing speciﬁcity. Pacing Clin Electrophysiol. 2007;30:748–754.


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